

Thyroglobulin Level as a Predictive Factor of Tumoral Recurrence in Differentiated Thyroid Cancer

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Ninety-eight patients with differentiated thyroid carcinoma were studied. Actuarial methods were used to investigate the 10-yr probability of survival (pS) and disease-free survival (pDFS). Our results show that the pDFS is a function of: (1) clinicopathologic stage: Stages I-II, pDFS = 90.9% \pm 5.0% versus Stages III-IV, pDFS = 55.9% \pm 17.8% ($p < 0.005$); (2) age: Age < 45 yr, pDFS = 87.2% \pm 10.0% versus age ≥ 45 yr, pDFS = 66.6% \pm 12.0% ($p < 0.002$); and (3) plasma thyroglobulin (Tg) levels: Tg ≤ 23 ng/ml, pDFS = 100% versus Tg > 23 ng/ml, pDFS = 68.3% \pm 10.6% ($p < 0.005$). Using the multivariate analysis of proportional risk, the regression coefficients obtained (Stage: $\beta = 0.7615$; Age: $\beta = 1.6398$, and Tg: $\beta = 1.7607$) allowed us to establish two different groups of risk of relapse on the basis of a prognostic index.

J Nucl Med 1991; 32:395-398

Previous reports (1-4) have shown that the quantification of serum levels of thyroglobulin (Tg) constitutes a method for clinical surveillance of patients with differentiated thyroid cancer (DTC). This approach permits the reliable early detection of local and regional recurrences or tumor metastases. Measurements of Tg in the immediate postoperative period in DTC patients provide information on the effectiveness of surgery in controlling the primary disease (5). In addition, studies of the kinetics of the disappearance of Tg in serum after metabolic radiotherapy have demonstrated differences that may be attributable to the presence of residual normal thyroid tissue following surgery or to residual tumoral thyroid tissue (6).

In this paper, we studied the evolution of a wide range of patients with DTC diagnosed and treated between 1977 and 1988 at the University of Granada Hospital. The overall aim of this research was to identify, among the different variables of known prognostic

significance, those parameters with greatest discriminative power in the prediction of individual prognoses. In the group of variables to be analyzed, we included data on serum Tg levels quantified 4 wk after surgical intervention as the initial treatment in DTC patients before they received any other treatment such as ablative ^{131}I therapy, adjuvant therapy, or hormonal substitution.

MATERIALS AND METHODS

Patients

Ninety-eight patients with DTC were studied (66% had papillary carcinoma and 33% had follicular carcinoma). There were 19 males and 79 females with DTC in different stages of clinical evolution. The mean age in our patients was 42 yr (range 13-77 yr), and 61% of the population was younger than 45 yr at the time of diagnosis and initial treatment. From a clinical standpoint, 80% of the patients had nodular goiter.

All patients were treated surgically with one of the following options: hemithyroidectomy (14 cases), subtotal thyroidectomy (52 cases), and apparent total thyroidectomy (32 cases). Cervical lymph node dissection (essentially nonradical homolateral) was performed on 32 patients. On the basis of clinicopathologic stages (7), 74% of the carcinomas were Stages I-II and 26% were Stages III-IV.

Serum Tg levels were determined by radioimmunoassay in the postoperative period in all patients (before ablative or hormone substitution therapy was begun) in accordance with a previously described procedure (8). After determining the upper threshold of normality in our laboratory as 23 ng/ml, 56% of our patients were found to have elevated levels of serum Tg.

The mean duration of follow-up was 44 mo (range 1-143 mo). At the end of the study, 81 patients were free of disease, 7 had recurrent disease, 3 had died from the tumor, and 7 patients from the initial group were lost to follow-up. Table 1 shows the distribution of our patients on the basis of clinical characteristics of their disease.

Variables of Prognostic Significance Analyzed

The search for the best prognostic criteria possible led us to analyze the significance of the following variables: age, sex, clinicopathologic stage, surgical treatment used, elective dissection of cervical lymph nodes, histologic typing of the tumor, and plasma Tg level.

Received May 9, 1990; revision accepted Aug. 21, 1990.
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TABLE 1
General Characteristics of the Series of 98 Patients with DTC

1. Age	<45 yr	60
	≥45 yr	38
2. Clinical features	Solitary nodules	80
	Multinodular goiter	4
	Diffuse goiter	4
	Not known	9
	Palpable lymph node	19
3. Histologic type	Papillary (*)	65
	Follicular (**)	33
4. Clinicopathologic stage	Stages I-II	73
	Stages III-IV	25
5. Serum Tg concentration	Normal (≤23 ng/ml)	43
	Elevated (>23 ng/ml)	55
6. Complementary treatment	¹³¹ I Therapy	66
	Thyroid hormone	98

* Mixed carcinomas included.
† Four Hurtle cell carcinomas included.

Statistical Methods

We calculated the overall probability of survival (pS), and the probability of disease-free survival (pDFS) [Kaplan-Meier method (9)] for the entire series of patients included in the study and for each of the subgroups classified on the basis of the variables in Table 1. The survival curves were compared with Mantel-Haenszel's test (10, 11). To determine the influence of the factors mentioned above on disease prognosis, we applied multivariate analysis of Cox's estimate of proportional risk (12).

RESULTS AND DISCUSSION

The overall probability of survival after 10 yr of follow-up in our series of patients was calculated as $93.7\% \pm 4.0\%$. No significant differences were seen between any of the subgroups in any of the variables analyzed as prognostic determinants. The data for pDFS showed that 10 yr after the initial treatment $79.5\% \pm 8.1\%$ of all patients were disease-free.

The probability of tumoral recurrence during this period was conditioned by the following factors:

1. Clinicopathologic stage. At the end of the follow-up period, $90.9\% \pm 5.0\%$ of the patients classified as Stages I-II were disease-free, while only $55.9\% \pm 17.8\%$ of the Stages III-IV patients were disease-free. Comparison of the survival curves for each subgroup (Fig. 1), showed a significant difference ($p < 0.005$).
2. Age. pDFS was higher in the subgroup of patients younger than 45 yr of age ($87.2\% \pm 10\%$) in comparison to the subgroup of patients above 45 (66.6%

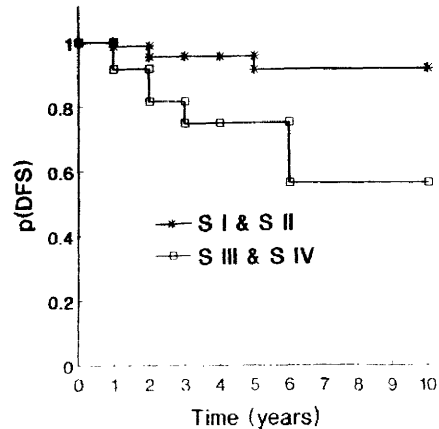


FIGURE 1
Actuarial pDFS by clinicopathologic stage. Stages I and II versus stages III and IV. Statistically significant difference is noted ($p < 0.005$).

- $\pm 12\%$). The differences between the survival curves for the two subgroups was also statistically significant ($p < 0.002$) (Fig. 2).
3. Thyroglobulin. Subdivision of the patients into two categories (normal/abnormal) on the basis of plasma Tg levels was an useful predictor of tumoral recurrence. One hundred percent of the patients in the subgroup with $Tg \leq 23$ ng/ml were disease-free whereas only $68.3\% \pm 10.6\%$ of the subgroup with Tg levels above this figure were free of clinical tumoral disease after 10 yr of follow-up ($p < 0.005$) (Fig. 3).
 4. Other variables. No difference in prognosis could be determined on the basis of type of surgical intervention, elective dissection of the cervical lymph nodes, sex, or histologic tumor type.

To investigate the relationship between the different factors which condition prognosis and the relative

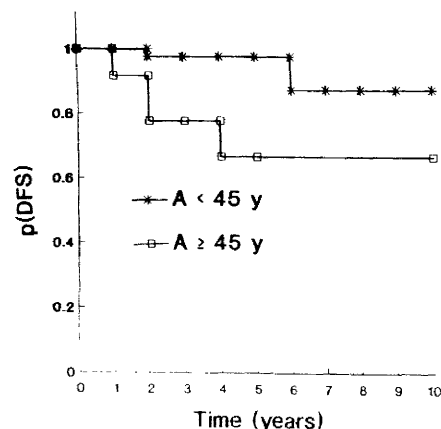


FIGURE 2
Actuarial pDFS by age. Age < 45 yr versus age ≥ 45 yr. Statistically significant difference is noted ($p < 0.002$).

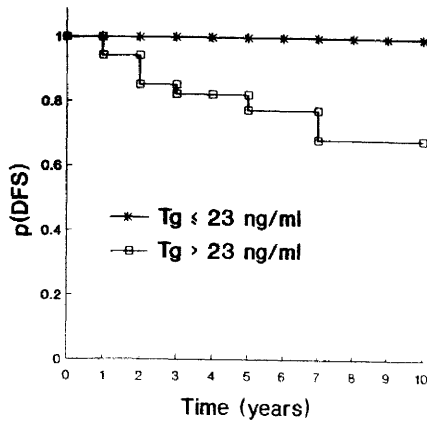


FIGURE 3
Actuarial pDFS by plasma thyroglobulin levels. Tg \leq 23 ng/ml versus Tg $>$ 23 ng/ml. Statistically significant difference is noted ($p < 0.005$).

weights of each factor, we used a multivariate analysis of proportional risk. First, we applied Cox's model and defined the dependent variable, which was DFS in this case. Second, we transformed the independent variables, or covariables, into categories defined by a code number (0, 1, . . . n). Zero was assigned as the most favorable category of prognosis and subsequent numbers indicated progressively less favorable prognoses. In this study, we used a binary code (0, 1) for all factors except clinicopathological stage, which was coded as follows: 0 = Stage I, 1 = Stage II, 2 = Stage III, and 3 = Stage IV.

Under these conditions, the parameters found to influence prognosis were: Age (regression coefficient $\beta = 1.6398$); clinicopathological stage ($\beta = 1.7615$); and plasma Tg concentration ($\beta = 1.7607$). All three variables had a statistically significant effect on the pDFS ($p < 0.05$).

Table 2 presents the risk indices calculated from the beta coefficients. Taking 1 as the risk of tumoral recurrence when age is $<$ 45 yr, the tumor was Stage I and Tg was \leq 23 ng/ml. We found that the risk of recurrence increased with patient age (\geq 45 yr), with more advanced clinicopathologic stages, and with above-normal levels of plasma Tg in the immediate postoperative period.

TABLE 2
Estimate of Proportional Risk (DFS) in DTC

Age	Stage	Tg	Risk	Age	Stage	Tg	Risk
0	0	0	1.00	1	0	0	5.15
0	0	1	5.81	1	0	1	29.97
0	1	0	2.14	1	1	0	11.03
0	1	1	12.45	1	1	1	64.19
0	2	0	4.58	1	2	0	23.63
0	2	1	26.67	1	2	1	137.48
0	3	0	9.82	1	3	0	50.61
0	3	1	57.12	1	3	1	294.41

On the basis of the risk indices shown in Table 2, patients can be classified into two different subgroups:

- 1. Low Risk group (score \leq 10)**
Age $<$ 45 yr, Stage I, any Tg level
Age $<$ 45 yr, Stages II, III and IV, Tg \leq 23 ng/ml
Age \geq 45 yr, Stage I, Tg \leq 23 ng/ml
- 2. Moderate Risk Group (Score $>$ 10)**
Age $<$ 45 yr, Stages II, III, and IV, Tg $>$ 23 ng/ml
Age \geq 45 yr, any stage, Tg $>$ 23 ng/ml

Based on these characteristics, we classified 59 of our 98 patients as low risk. The pDFS estimated by the Kaplan-Meier procedure was 86% at 10 yr. The same estimate in the subgroup of 39 patients classified as moderate risk yielded a 66% probability (Fig. 4). As the Mantel-Haenszel (log-rank) comparison of the DFS curves for each subgroup was clearly significant ($p < 0.001$), it is clear that plasma Tg in the immediate postoperative period, as well as age and clinicopathologic stage of the disease at the time of initial treatment, were the factors of greatest weight in predicting the long-term prognosis in our DTC patients. Vathaire et al. (13) have recently demonstrated similar results on the usefulness of serum Tg as a predictor of tumoral recurrence in DTC patients. Multivariate analysis of survival in our series of 98 patients only revealed the influence of age and clinicopathologic stage as factors predictive of the risk of death. A study of the patients over a longer follow-up period would probably allow us to determine the actual influence of other parameters on disease prognosis in our population.

This procedure for calculating thyroid cancer prognoses has been used by others (14-19). In general, the studies published to date disagree on the definition of weighting factors that influence prognosis and on the quantification of the risk associated with each factor.

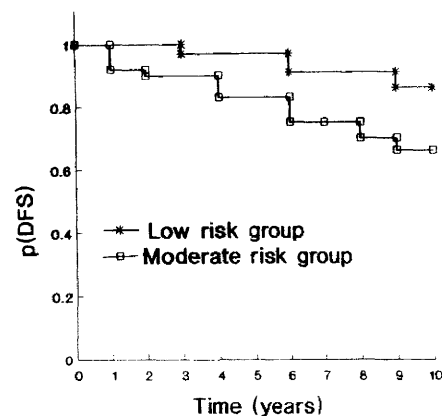


FIGURE 4
Actuarial pDFS by low and moderate established groups. Low risk group versus moderate risk group. Statistically significant difference is noted ($p < 0.01$).

The main cause of these discrepancies [also noted in studies of other tumoral processes, e.g., Balch (20) and Bosl (21)] seems to be rooted in the epidemiologic differences between the study populations. Hannequin (17), using the Cox's regression model for analyzing the results of several studies, found non-comparable results for the identification of significant prognostic factors and the estimation of regression coefficients obtained in different series of patients and concluded that in order for the model to be truly useful specific risk indices have to be calculated for each individual population.

ACKNOWLEDGMENTS

This study was supported by grant 4111-85 from the Comisión Asesora para la Investigación Científica y Técnica (CAICYT). Spanish Ministry of Education and Science.

The authors thank Ms. Karen Shashok for translating the original manuscript into English.

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